# Diagnosi differenziale tra Malattia di Alzheimer e Demenza Fronto-Temporale

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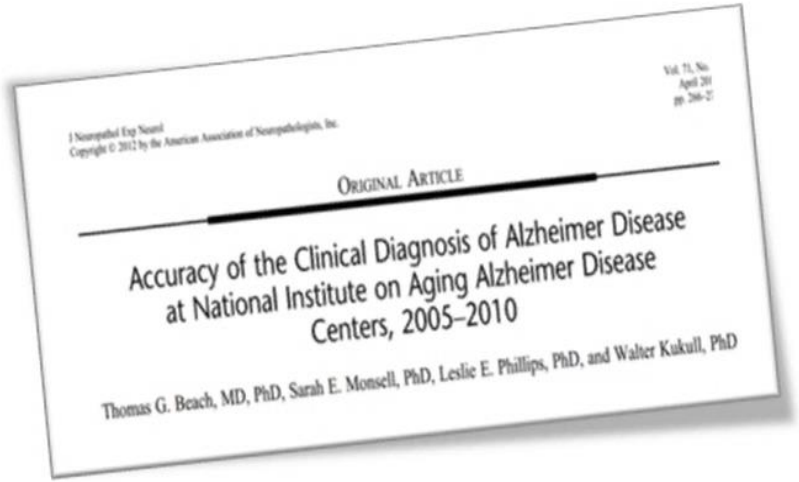
Centro Regionale di Neurogenetica, ASP-CZ



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ORIGINAL ARTICLE

# Accuracy of the Clinical Diagnosis of Alzheimer Disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010

Thomas G. Beach, MD, PhD, Sarah E. Monsell, PhD, Leslie E. Phillips, PhD, and Walter Kukull, PhD



**TABLE 2.** Sensitivity and Specificity of the Clinical Diagnosis of AD Relative to Stratified Clinical Confidence Levels and Minimum Threshold Levels for Histopathologic Severity

| Neuropathologic AD Definition | Clinically Probable AD, n = 526 | Clinically Probable or Possible AD, n = 648 |
|---|---|---|
| CERAD NP Freq | n = 327 | n = 373 |
| Braak Stage V or VI | Sensitivity 76.6% | Sensitivity 87.3% |
| n = 427 | Specificity 59.5% | Specificity 44.3% |
| CERAD NP Mod or Freq | n = 366 | n = 418 |
| Braak Stage V or VI | Sensitivity = 75.3% | Sensitivity = 85.9% |
| n = 486 | Specificity = 63.0% | Specificity = 47.0% |
| CERAD NP Freq | n = 370 | n = 421 |
| Braak Stage III–VI | Sensitivity = 75.5% | Sensitivity = 85.9% |
| n = 490 | Specificity = 63.6% | Specificity = 47.1% |
| CERAD NP Mod or Freq | n = 438 | n = 511 |
| Braak Stage III–VI | Sensitivity = 70.9% | Sensitivity = 82.7% |
| n = 618 | Specificity = 70.8% | Specificity = 54.5% |

Histopathological severity is determined by specific combinations of CERAD NP and Braak neurofibrillary stage.

AD, Alzheimer disease; CERAD NP, Consortium to Establish a Registry for Alzheimer's Disease neuritic plaque density score; Mod, moderate; Freq, frequent; Braak Stage, Braak neurofibrillary tangle stage.

**TABLE 4.** Primary Neuropathologic Diagnosis for the 88 Subjects Clinically Diagnosed as Probable AD But Not Meeting a Defined Minimum Threshold Level of Histopathologic Severity

| Primary Neuropathologic Findings | No. Cases |
|---|---|
| Primary neuropathologic diagnosis of AD despite low level of AD histopathology | 17 |
| Tangle-only dementia or argyrophilic grain disease | 15 |
| Frontotemporal lobar degeneration* | 15 |
| Cerebrovascular disease | 10 |
| Lewy body disease, with or without AD† | 9 |
| Hippocampal sclerosis, with or without AD‡ | 9 |
| Progressive supranuclear palsy | 3 |
| Corticobasal degeneration | 2 |
| Neuroaxonal dystrophy/Hallervorden-Spatz-like condition | 2 |
| Miscellaneous (1 case each of amyloid angiopathy, "small vessel disease," "TDP-43 proteinopathy," limbic encephalitis, Rosenthal fiber encephalopathy, "clinical dementia, no neuropathological substrate") | 6 |

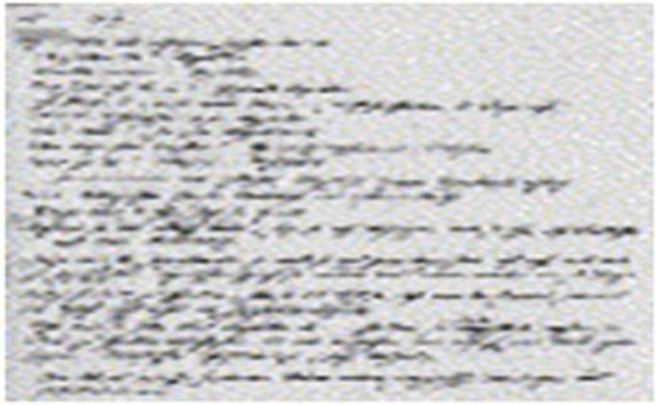
Criteria for Alzheimer disease (AD) diagnosis were based on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaque density of moderate or frequent in combination with any Braak neurofibrillary tangle stage between III and VI, inclusive.

*Of cases with frontotemporal lobar degeneration, 7 had ubiquitin or TDP-43–positive inclusions; 3 had tauopathies.

†Of cases with primary Lewy body disease, 2 also had a contributory diagnosis of AD.

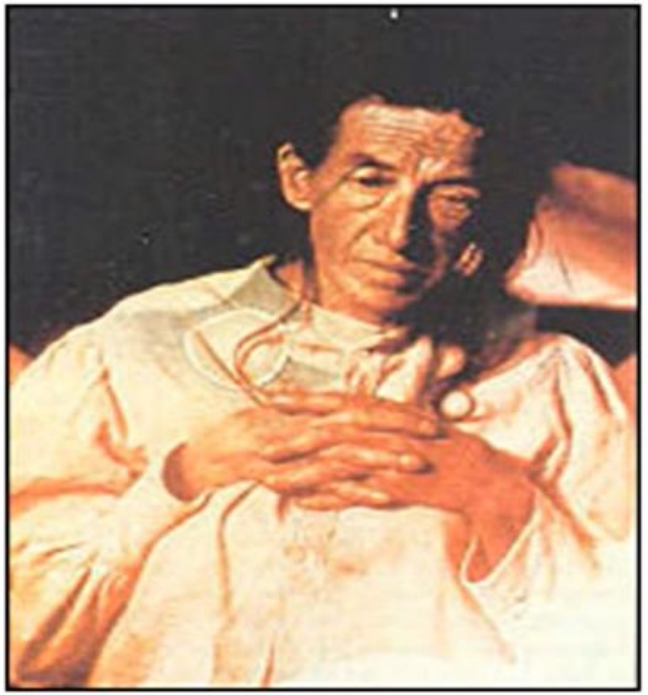
‡Of cases with primary hippocampal sclerosis, 1 also had a contributory diagnosis of AD.

# Background



*"… as one of her first disease symptom was a strong feeling of jealously towards her husband. Very soon she showed rapidly increasing memory impairment; she was disoriented carrying objects to and for in her flat and hid them. Sometimes she felt that someone wanted to kill her and began to scream loudly…After 4 ½ years of sickness she died."*

*Alois Alzheimer, 1907*



Auguste D., 51 y/o

# Distinct clinical and pathological characteristics of frontotemporal dementia associated with *C9ORF72* mutations

| ID | Sex | Age at onset (years) | Years onset to referral | death | Family history FTD | Family history MND | Family members affected | Clinical classification at presentation | Dominant presenting problem |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 54 | <1 | ? | – | + | Two brothers | FTD/MND | Speech production |
| 2 | F | 54 | 1 | 1 | + | – | Sister | FTD/MND | Speech production |
| 3 | F | 72 | 1 | 2 | – | – | – | FTD/MND | Speech production |
| 4 | M | 58 | <1 | ? | ? | ? | ? | FTD/MND | Speech production |
| 5 | M | 57 | <1 | ? | + | – | Father | FTD/MND | Psychosis |
| 6 | F | 68 | 4 | 5 | + | + | Brother FTD, sister MND | FTD/MND | Psychosis |
| 7 | F | 70 | 1 | ? | + | + | Two sisters FTD-MND; mother, son and daughter MND | FTD/MND | Behaviour |
| 8 | M | 58 | 1 | 2 | – | – | | FTD/MND | Behaviour |
| 9 | M | 57 | 1 | 2 | + | – | Mother, uncle | FTD/MND | Behaviour |
| 10 | M | 49 | 6 | 9 | + | – | Four sibs | FTD | Psychosis |
| 11 | M | 55 | 1 | ? | + | + | Mother (FTD-MND) | FTD | Psychosis |
| 12 | M | 64 | 1 | ? | + | – | Father, brother, three aunts | FTD | Psychosis |
| 13 | M | 65 | 2 | ? | + | – | Father | FTD | Psychosis |
| 14 | F | 53 | <1 | ? | – | – | – | FTD | Psychosis |
| 15 | M | 58 | 3 | ? | – | – | – | FTD | Behaviour |
| 16 | M | 62 | 10 | ? | + | – | Brother-dementia, father- parkinsonian | FTD | Behaviour |
| 17 | M | 68 | 5 | ? | – | – | – | FTD | Behaviour |
| 18 | M | 39 | 1 | ? | + | – | Mother[a], grandfather | FTD | Behaviour |
| 19 | M | 70 | 2 | ? | – | – | – | FTD | Behaviour |
| 20 | F | 52 | 10 | ? | + | – | Mother, sister | FTD | Behaviour/psychosis |
| 21 | M | 55 | 4 | ? | + | – | Father, uncle | FTD | Behaviour |
| 22 | F | 62 | | ? | + | + | Mother, uncle, grandmother (dementia), brother (MND) | FTD | Behaviour/psychosis |
| 23 | M | 46 | 2 | ? | + | – | Mother | FTD | Behaviour/psychosis |
| 24 | M | 59 | 4 | 11 | –[b] | – | – | FTD | Behaviour/psychosis |
| 25 | M | 55 | 2 | ? | – | – | – | FTD | Behaviour |
| 26 | F | 72 | 1 | ? | – | – | – | FTD | Behaviour |
| 27 | M | 56 | 4 | ? | + | – | Mother, grandparent | FTD | Psychosis |
| 28 | F | 60 | 1 | 6 | + | – | Father, son[c] | FTD | Behaviour |
| 29 | F | 47 | 3 | ? | + | – | Mother | SD/FTD | Language/behaviour |
| 30 | F | 52 | 1 | 4 | – | – | – | PNFA | Expressive language |
| 31 | F | 62 | 2 | 4 | + | – | Mother | PNFA | Expressive language |
| 32 | F | 58 | 4 | ? | – | – | – | PNFA | Expressive language |

A striking and unanticipated finding was the **strong association of C9ORF72 gene mutations with psychotic symptoms**: delusions, hallucinations, paranoid ideation and disordered thinking.

More than **a third of patients presented with florid psychosis** and were initially classified by their psychiatrist using conventional psychiatric diagnostic labels: delusional psychosis, mono-delusional psychosis, somatoform psychosis, paranoid schizophrenia.

Other patients exhibited paranoid and delusional thinking as part of their behavioural disorder. **In two-thirds of patients behaviour was bizarre and illogical**. None of these patients had a history of psychiatric illness.

The high prevalence of psychotic symptomatology is important because of its rarity in FTD in general

# Le varianti cliniche della FTD

**Behavioural variant FTD**

- **Apathetic Variant**
- **Disinhibited Variant**
- **Psychotic Variant**

**Semantic Dementia**

**Progressive Non-Fluent Aphasia**

- **Logopenic Variant**

Apraxic

FTD Parkinsonism

FTD-MND

**Amnesic**

# Le varianti cliniche della M. Alzheimer

Amnesica

PCA

**Semantica**

**PPA/Logopenica**

**Motoria/Aprassica**

**Comportamentale/Frontale**

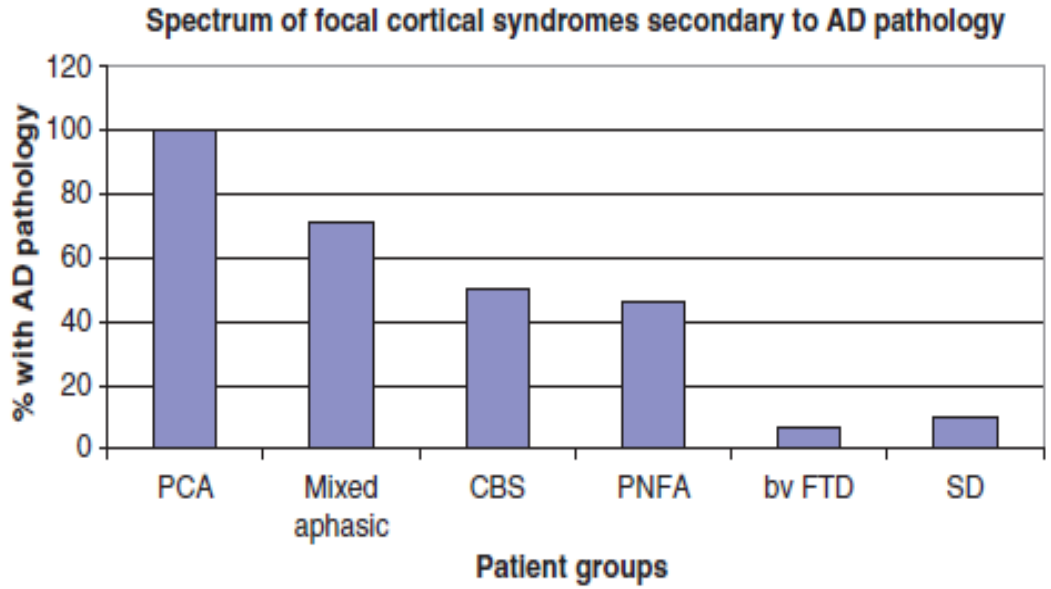
**Psicotica**

**Variante Lewy**

doi:10.1093/brain/awm213 *Brain* (2007), **130**, 2636–2645

# Focal cortical presentations of Alzheimer's disease

S. Alladi,[1] J. Xuereb,[2] T. Bak,[1] P. Nestor,[1] J. Knibb,[1] K. Patterson[3] and J. R. Hodges[1,3]




AD pathology is frequently found in patients with atypical cortical syndromes, suggesting that diagnosis of AD needs to be considered even in patients who present with focal dementia without significant memory loss, especially in cases with PCA, CBS and PNFA.

ORIGINAL CONTRIBUTION

# Distinct Antemortem Profiles in Patients With Pathologically Defined Frontotemporal Dementia

*Murray Grossman, MD; David J. Libon, PhD; Mark S. Forman, MD, PhD; Lauren Massimo, LPN; Elisabeth Wood, MS; Peachie Moore, BA; Chivon Anderson, BA; Jennifer Farmer, MS; Anjan Chatterjee, MD; Christopher M. Clark, MD; H. Branch Coslett, MD; Howard I. Hurtig, MD; Virginia M.-Y. Lee, PhD, MBA; John Q. Trojanowski, MD, PhD*

*Arch Neurol. 2007;64(11):1601-1609*

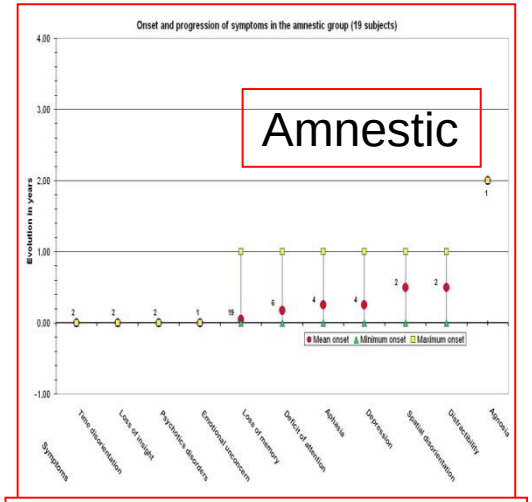
36% 41% 23%

| Characteristic | Tau-Positive FTD (n=22) | Tau-Negative FTD (n=25) | Frontal-Variant AD (n=14) |
|---|---|---|---|
| Age at initial evaluation, mean (SD), y | 64.73 (11.9) | 64.64 (9.5) | 69.79 (11.3) |
| Educational level, mean (SD), y | 16.00 (2.5) | 14.56 (2.6) | 15.43 (2.2) |
| MMSE score, mean (SD) (maximum score=30) | 19.18 (8.3) | 22.65 (6.9) | 21.86 (4.8) |
| Duration of illness, mean (SD), mo | 37.14 (26.8) | 31.91 (28.2) | 46.71 (36.0) |
| Clinical phenotype at diagnosis, No. | | | |
| Progressive nonfluent aphasia | 5 | 2 | 2 |
| Semantic dementia | 0 | 3 | 1 |
| Progressive mixed aphasia | 0 | 3 | 2 |
| Social or executive disorder | 7 | 15 | 2 |
| Corticobasal syndrome | 8 | 0 | 2 |
| AD | 1 | 2 | 0 |
| Vascular dementia | 0 | 0 | 1 |
| Lewy body disease | 1 | 0 | 0 |
| Pathologic diagnosis, No. | | | |
| Pick disease | 3 | 0 | 0 |
| Corticobasal degeneration | 12 | 0 | 0 |
| Argyrophilic grain disease | 2 | 0 | 0 |
| Progressive supranuclear palsy | 2 | 0 | 0 |
| Other tau-positive disorders[b] | 3 | 0 | 0 |
| FTLD-U | 0 | 22 | 0 |
| Other tau-negative disorders[c] | 0 | 3 | 0 |
| Frontal-variant AD | 0 | 0 | 14 |

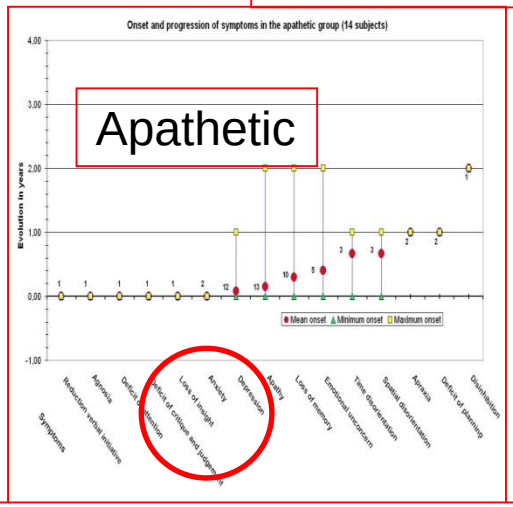
# Worldwide distribution of *PSEN1* Met146Leu mutation

## A large variability for a founder mutation

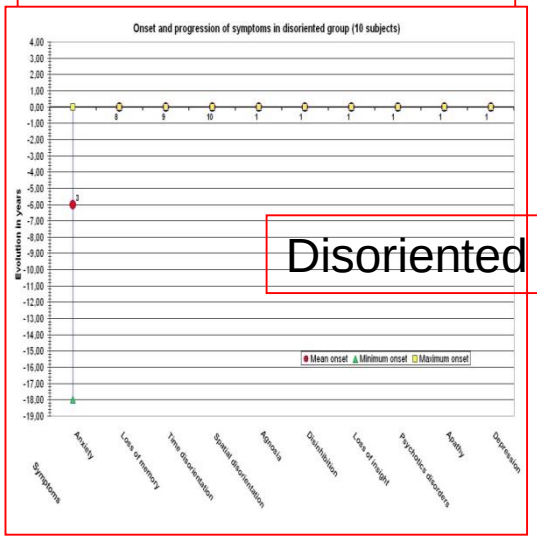
Neurology 2010



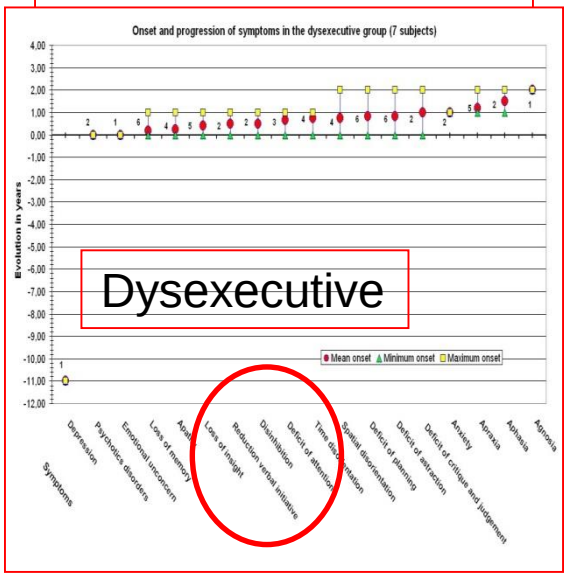

Amnestic




Apathetic




Disoriented




Dysexecutive

Onset presentation in M146L FAD patients

ELSEVIER

Neurobiology of Aging 33 (2012) 2948.e1–2948.e10

NEUROBIOLOGY OF AGING

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Genetic Reports Abstracts

# Epidemiology and genetics of frontotemporal dementia: a door-to-door survey in Southern Italy

Livia Bernardi[a,1], Francesca Frangipane[a,1], Nicoletta Smirne[a,1], Rosanna Colao[a], Gianfranco Puccio[a], Sabrina A.M. Curcio[a], Maria Mirabelli[a], Raffaele Maletta[a], Maria Anfossi[a], Maura Gallo[a], Silvana Geracitano[a], Maria Elena Conidi[a], Raffale Di Lorenzo[a], Alessandra Clodomiro[a], Chiara Cupidi[a], Sandra Marzano[b], Francesco Comito[b], Vincenzo Valenti[b], Maria Angela Zirilli[b], Mahdi Ghani[c], Zhengrui Xi[c], Christine Sato[c], Danielle Moreno[c], Annelisa Borelli[d], Rosa Anna Leone[d], Peter St. George-Hyslop[c,e,f], Ekaterina Rogaeva[c,e], Amalia C. Bruni[a,*]

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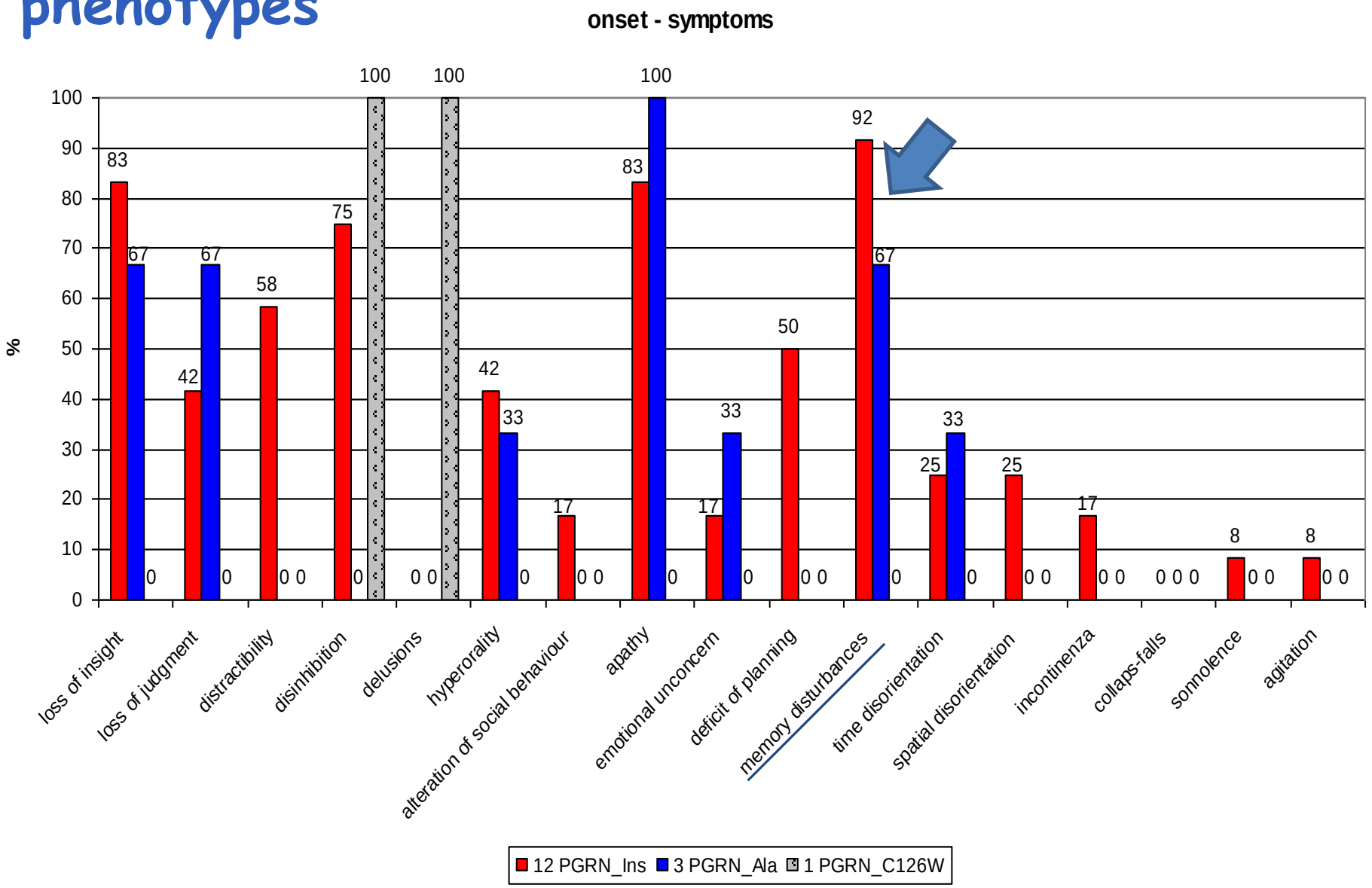
**Abstract**

The objectives of this study were to estimate frontotemporal dementia (FTD) prevalence, identify FTD-related mutations, and correlate FTD phenotype with mutations in a Southern Italian population. The study population consisted of subjects ≥ 50 years of age residing in the Community of Biv. on January 1, 2004, and a door-to-door 2-phase design was used. Genetic and biochemical analyses were done on samples collected from 32 patients. Prevalence rates were 0.6 for Alzheimer's disease, 0.4 for vascular dementia (VD), 3.5 for FTD, 0.2 for Parkinson dementia, and 1.2 for unspecified dementia. Three *GRN* (1 known and 2 novel) mutations with reduced plasma protein levels were found associated to 3 distinct phenotypes (behavioral, affective, and delirious type). We report an unusually high FTD prevalence in the investigated population, but a low prevalence of Alzheimer's disease. We confirm the heterogeneity of FTD phenotype associated with different *GRN* mutations.


*Keywords:* Door-to-door study; Frontotemporal dementia; Gene; Progranulin; Mutation; Prevalence studies

# PGRN mutations phenotypes



REVIEW

# Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Recent studies have gathered rich clinical data from large groups of subjects across a spectrum of cognitive states, correlated these clinical findings with new pathological markers at autopsy, and then analysed the data using powerful statistical methods. These studies have indicated that the diseases of aged human brains are complex: multiple comorbid pathologies are the norm, and there is substantial interindividual variation in neuropathological phenotypes

**The term LATE is intended to encompass several previously used designations related to TDP-43 proteinopathy that may be associated with cognitive impairment, including hippocampal sclerosis, hippocampal sclerosis of ageing, hippocampal sclerosis dementia, cerebral age- related TDP-43 with sclerosis, and TDP-43 pathologies in the elderly**

REVIEW

# Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

BRAIN 2019: 0; 1–25 | 1

- LATE-NC features
  - A sampling and staging system for routine autopsy diagnosis is proposed to characterize the anatomical distribution of TDP-43 proteinopathy
    - Stage 1: amygdala only
    - Stage 2: + hippocampus
    - Stage 3: + middle frontal gyrus
  - Hippocampal sclerosis pathology may be observed (and should be reported), but is neither necessary nor sufficient for diagnosis of LATE-NC
- LATE-NC is present in >20% (up to 50%) of individuals past age 80 years according to large community-based autopsy series
- LATE is associated with substantial disease-specific cognitive impairment, usually an amnestic dementia syndrome ('dementia of the Alzheimer's type')

- The overall public health impact of LATE is on the same order of magnitude as Alzheimer's disease neuropathological changes; the diseases are often comorbid, but which pathology is more severe varies greatly between individuals
- Genetic risk factors for LATE have some overlap with FTLD-TDP and with Alzheimer's disease
- There is no molecule-specific biomarker for LATE. This is an important area of need for use in clinical trials (including as a potential exclusion criterion for Alzheimer's disease clinical trials) and longitudinal studies of the clinical and pathological progression of LATE

LATE is among the common age-related diseases that can mimic the amnestic presentation of Alzheimer's disease (Nelson et al., 2013), and it is one of many reasons why biological rather than clinical disease definitions are important in the era of disease modifying clinical trials (Jack et al., 2018).

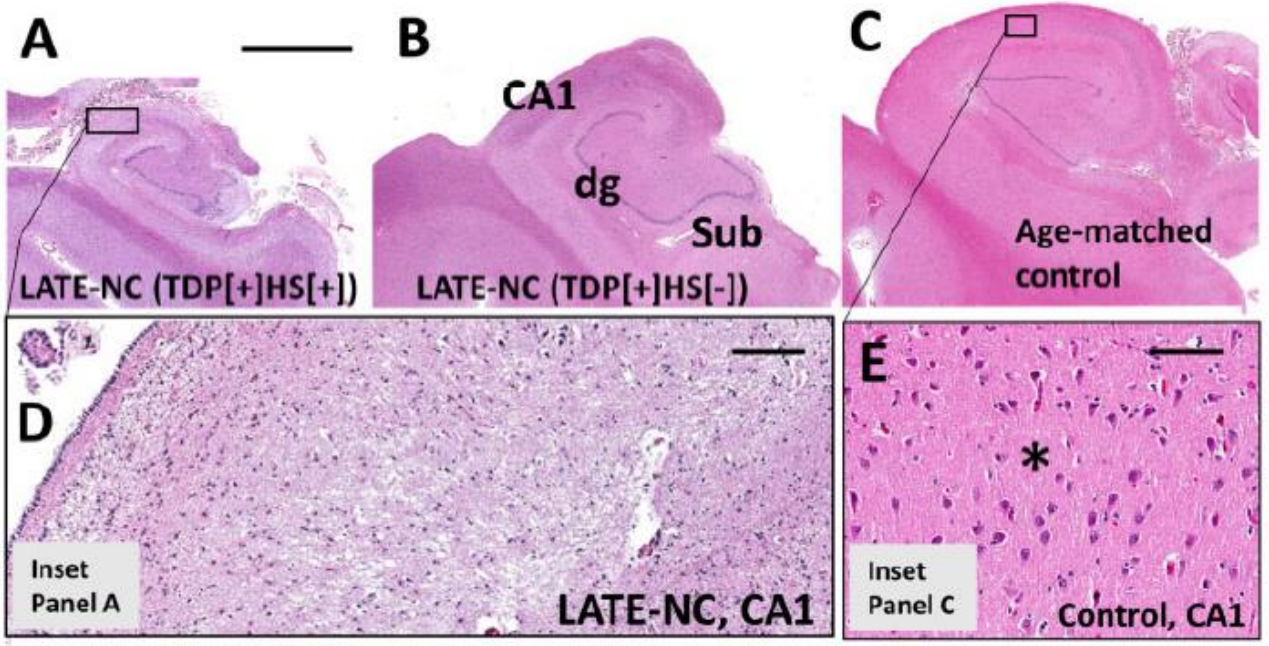



**Figure 1 LATE neuropathological changes (LATE-NC).** (**A**–**E**) Coronally sectioned human hippocampi stained using haematoxylin and eosin (H&E). Note that the photomicrographs in **A**–**C** are presented at the same magnification. (**A**) LATE-NC with hippocampal sclerosis (HS). The hippocampus is atrophic and the neuropil rarefied. (**D**) Higher magnification in CA1 subfield, with lack of normal cellular architecture and with extensive gliosis. (**C**) Control age-matched hippocampus. (**E**) CA1 of the control hippocampus to demonstrate the normal cellular architecture and intact eosinophilic neuropil (asterisk). The hippocampus shown in **B** is less atrophic, with less obvious neuropil disruption, in comparison to the case in **A** at low magnification; however, an adjacent section revealed TDP-43 proteinopathy. Hippocampal fields are labelled in **B**: dg = dentate granule layer; Sub = subiculum. TDP-43 proteinopathy can be recognized using antibodies raised against either non-phosphorylated or phosphorylated TDP-43 epitopes. (**F**) Dentate granule cells in a case lacking TDP-43 pathology. Note that cell nuclei are normally

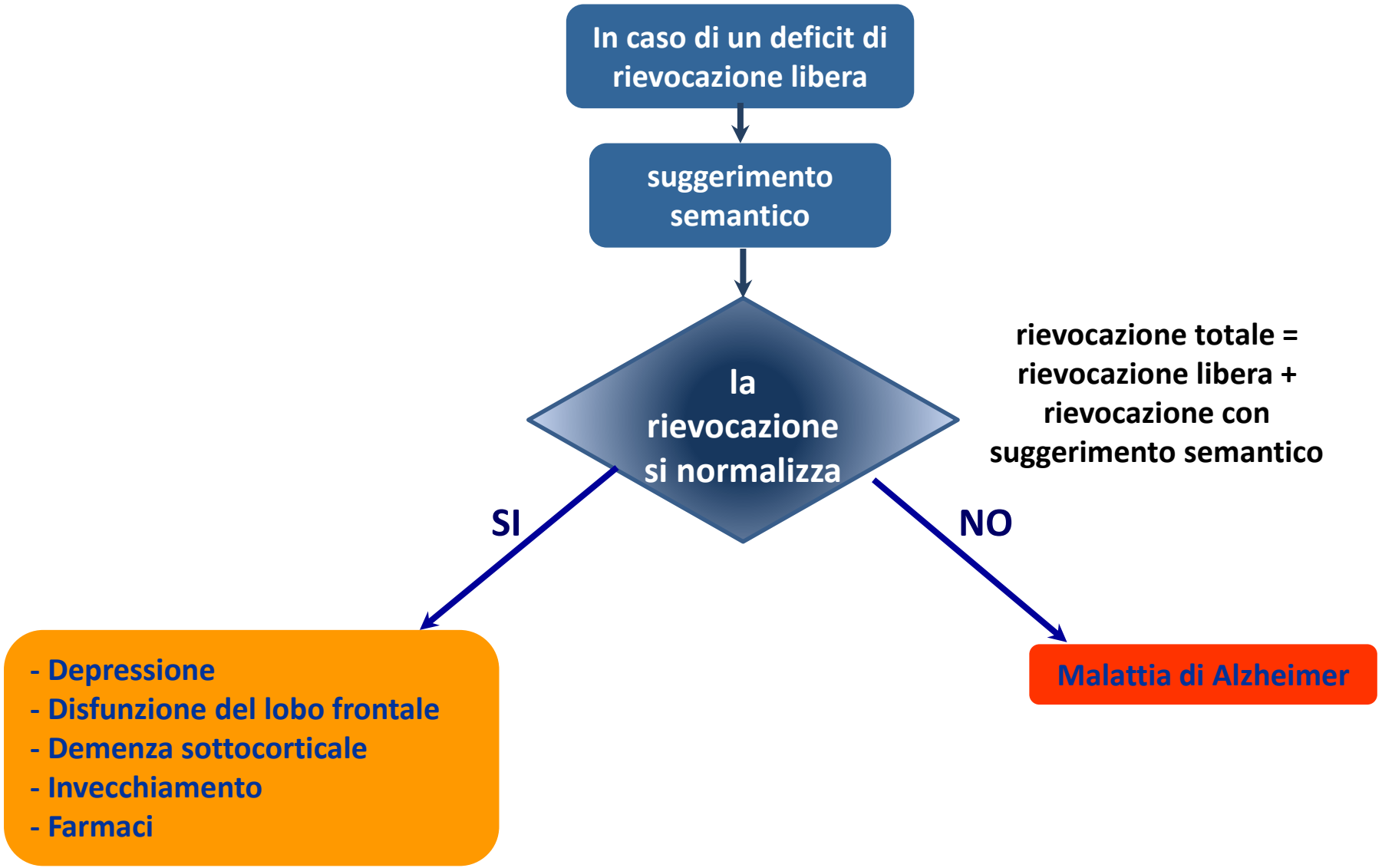
AD vs FTD

# SONO CLINICAMENTE DISTINGUIBILI?

# AD vs FTD

Come arrivare ad una diagnosi patogenetica?

# Tool Neuropsicologico: Memoria Ippocampale



Neuropsychol Rev (2011) 21:54–65
DOI 10.1007/s11065-010-9153-7

REVIEW

# Category Cued Recall Following Controlled Encoding as a Neuropsychological Tool in the Diagnosis of Alzheimer's Disease: A Review of the Evidence

Giovanni Augusto Carlesimo · Roberta Perri · Carlo Caltagirone

**Table 1** Summary of studies comparing individuals with AD and healthy controls (HCs) on the original (GB) or modified (RI48and DMT) version of the Grober-Buschke paradigm

| Authors | Sample size | | Dementia severity | Procedure | Free recall | | Total recall | | Other memory tests | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | HCs | AD | | | Sensitivity | Specificity | Sensitivity | Specificity | Test | Sensitivity | Specificity |
| Grober and Buschke, 1987 | 25 | 25[a] | DRS mean: 110 | GB Immediate | 88.0 | 92.0 | 96.0 | 100 | | | |
| Grober et al. 1988 | 48[b] | 22[c] | DRS mean: 113 | GB Immediate | 77.3 | 93.7 | 98.0 | 100 | | | |
| Buschke et al. 1997 | 90 | 30[d] | BIMC mean error score: 10.5 | DMT Immediate | – | – | 93.3 | 98.8 | Item Cued Recall | 53.3 | 94.4 |
| | | | | | | | | | Verbal paired associates immediate recall | 68.2 | 90.6 |
| | | | | | | | | | Logical memory immediate recall | 47.6 | 91.5 |
| Brown and Storandt 2000 | 73 | 24 | CDR=0.5 | DMT Immediate | | | 62.0 | 95.0 | Logical memory | 58.0 | 95.0 |
| | | 34 | CDR=1 | | | | 88.0 | 95.0 | | – | – |
| Ivanoiu et al. 2005 | 22[e] | 22 | MMSE: mean 23 | RI48 Immediate | – | – | 94.0 | 100 | Word list free recall | 100 | 86.0 |
| | | | | | | | | | Shape test recall | 94.0 | 94.0 |
| | | | | | | | | | Doors test | | |
| | | | | | | | | | Part A | 71.0 | 86.0 |
| | | | | | | | | | Part B | 64.0 | 86.0 |
| Saka et al. 2006 | 33 | 45 | MMSE: mean 18 | GB Immediate | 93.3 | 97.0 | 100 | 93.9 | | | |
| Vogel et al. 2007 | 28 | 35 | MMSE: mean 27 range 23–29 | DMT Immediate | | | 88.6 | 96.4 | ADAS memory test Immediate | 88.6 | 96.4 |
| | | | | Delayed | | | 91.4 | 96.4 | Delayed | 100 | 89.3 |

# Marker di presentazione neuropsicologica e nuovi criteri diagnostici della Malattia di Alzheimer

Per la prima volta viene definito uno specifico task mnesico potenzialmente patognomonico di identificare un la patologia tipo AD

**Prodromal AD (also called "predementia stage of AD")**

This term refers to the early symptomatic, predementia phase of AD in which (1) clinical symptoms including episodic memory loss of the hippocampal type (characterised by a free recall deficit on testing not normalised with cueing) are present, but not sufficiently severe to affect instrumental activities of daily living and do not warrant a diagnosis of dementia; and in which (2) biomarker evidence from CSF or imaging is supportive of the

Dubois et al., 2010

**Biomarkers indicativi di deposito di** Aβ

- Presenza nel liquor di Aβ 1-42
- PET con studio deposito di amiloide
- *Dosaggio plasmatico di Aβ 1-42*

**Biomarkers indicativi di Taupatia o FTD**

- Dosaggio PGRN plasma/CSF
- PET-Tau
- CSF TotaleTau/pTau
- TMS SICI/ICF

**Biomarkers indicativi di danno neuronale**

- Presenza nel liquor di proteina tau e tau fosforilata e di lcNFL
- Misure del volume ippocampale o MTLA
- Misure di atrofia cerebrale
- PET FDG
- TMS plasticity index

**ALTRI BIOMARKERS**

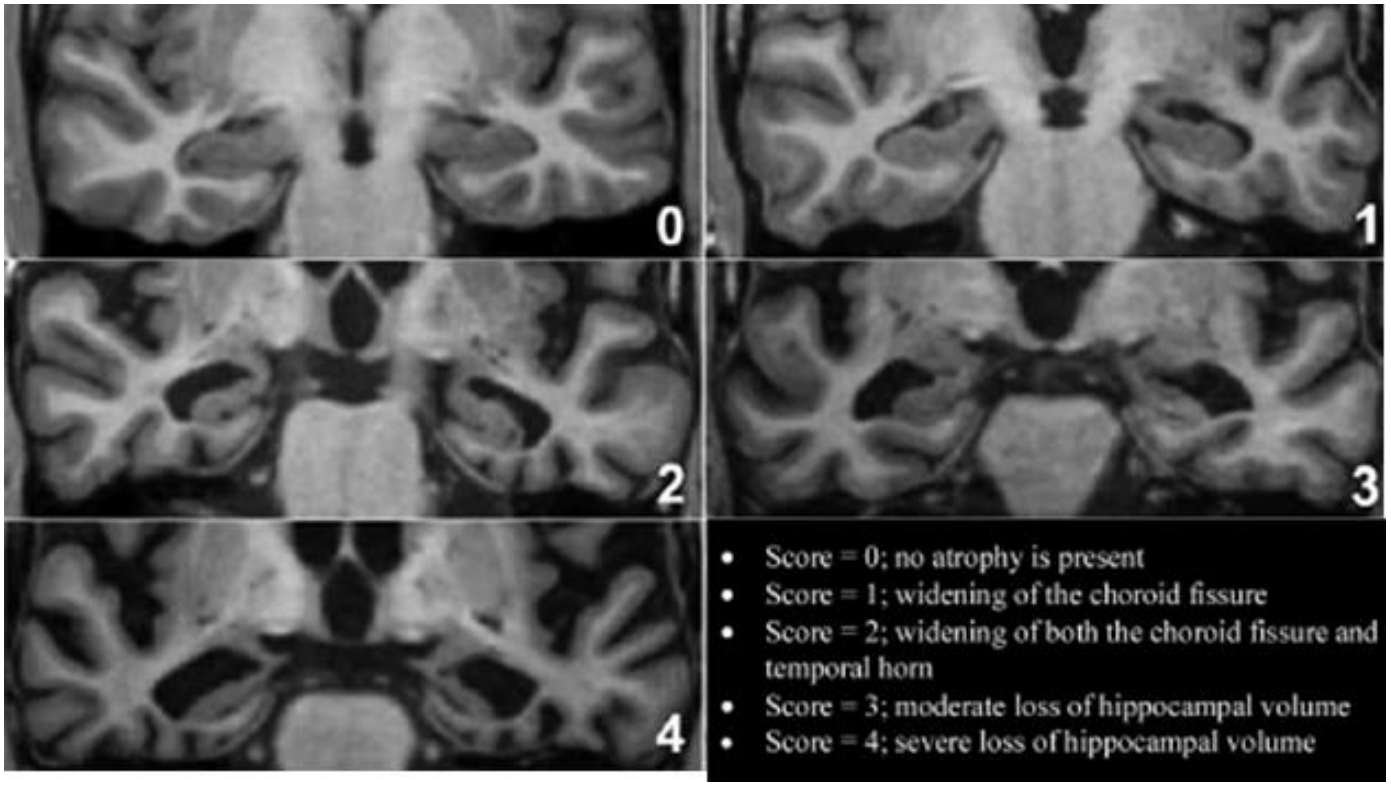
- DATSCAN
- fMRI
- EEG
- TMS SAI

# Differentiating between dementia etiologies

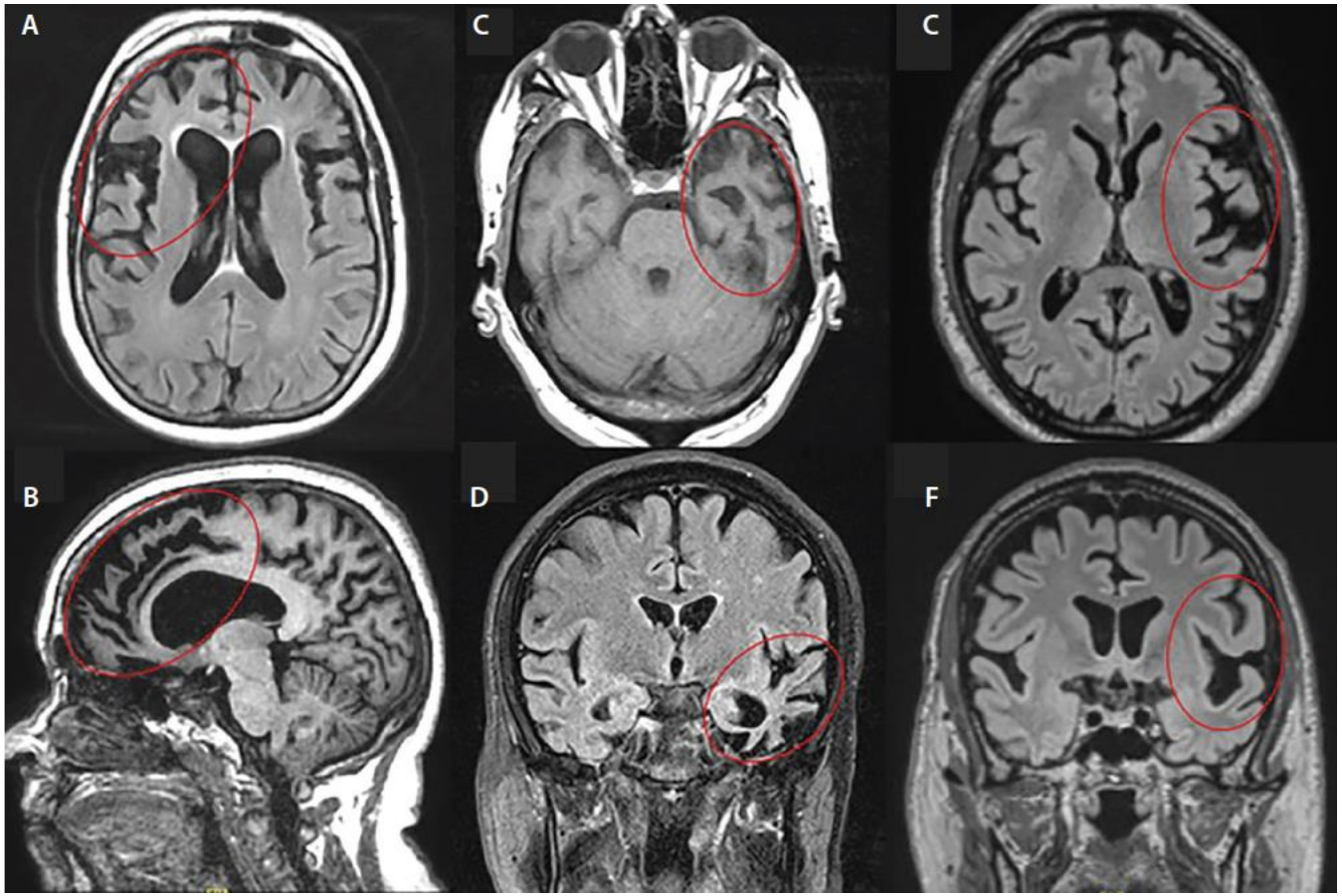
| Condition | Characteristic structural imaging findings |
|---|---|
| **Alzheimer's disease**[1] | • Medial temporal lobe atrophy<br>Parietal atrophy<br>Ventriculomegaly<br>• Global volume loss |
| **Behavioral frontotemporal lobar degeneration**[1] | • Frontal and anterior temporal atrophy<br>• Medial temporal lobe atrophy<br>Often asymmetry |
| **Vascular dementia**[1] | • Cortical and/or lacunar infarctions<br>Deep and periventricular white matter T2 hyperintensity / CT hypodensity<br>• Global volume loss<br>• Mild medial temporal lobe atrophy |
| **Dementia with Lewy bodies**[1] | • Global volume loss |
| **Hippocampal sclerosis**[2] | • Hippocampal atrophy* |
| **Multiple system atrophy**[3] | • Atrophy of putamen, middle cerebellar peduncle, pons and/or cerebellum |
| **Creutzfeldt–Jakob disease**[3] | • Cortical diffusion changes; pulvinar sign |

*hyperintensity in the hippocampal region on a T2 or FLAIR image can help to differentiate between AD[2]

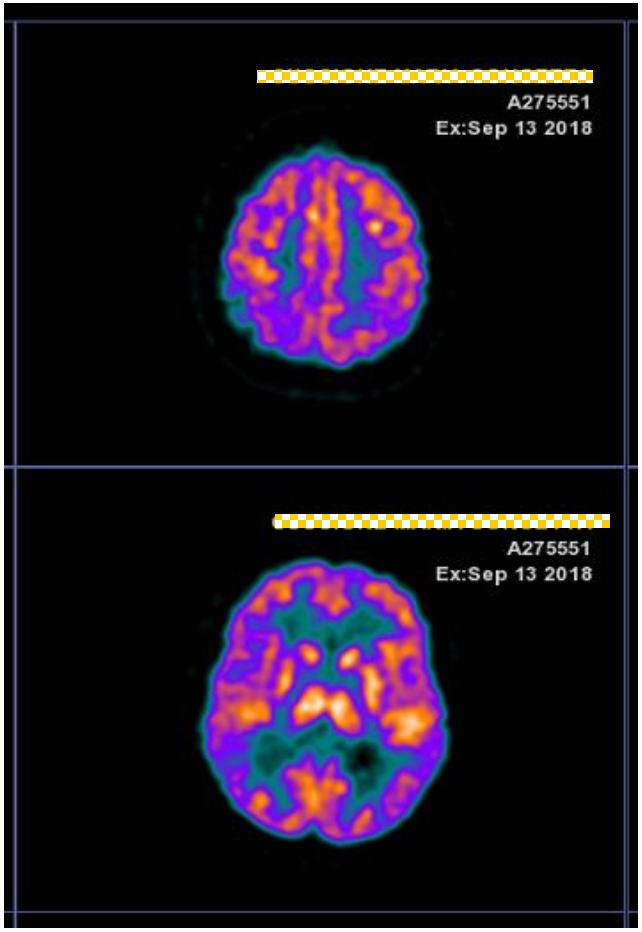
# RMN - AD


0
1
2
3
4
• Score = 0; no atrophy is present
• Score = 1; widening of the choroid fissure
• Score = 2; widening of both the choroid fissure and temporal horn
• Score = 3; moderate loss of hippocampal volume
• Score = 4; severe loss of hippocampal volume

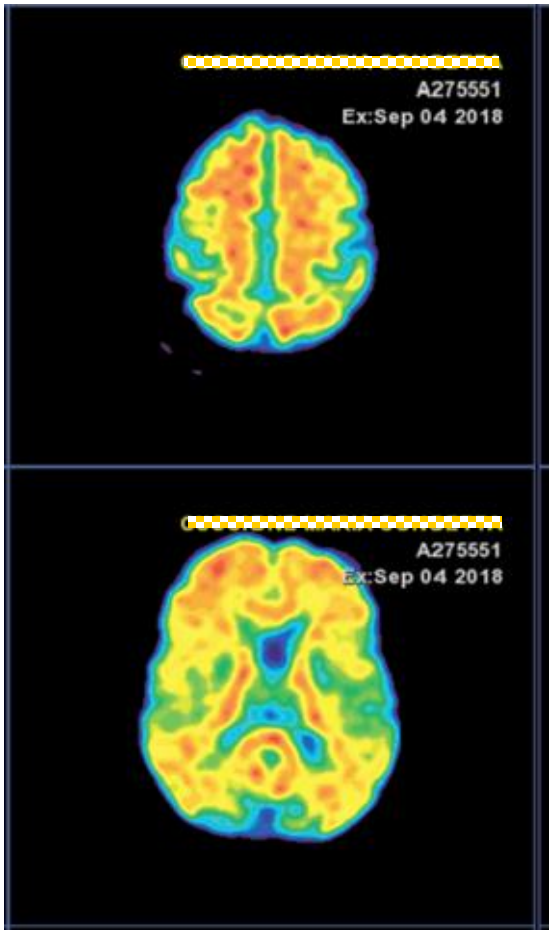
# RMN - FTD



# AD




FDG-PET




PET-Amiloide

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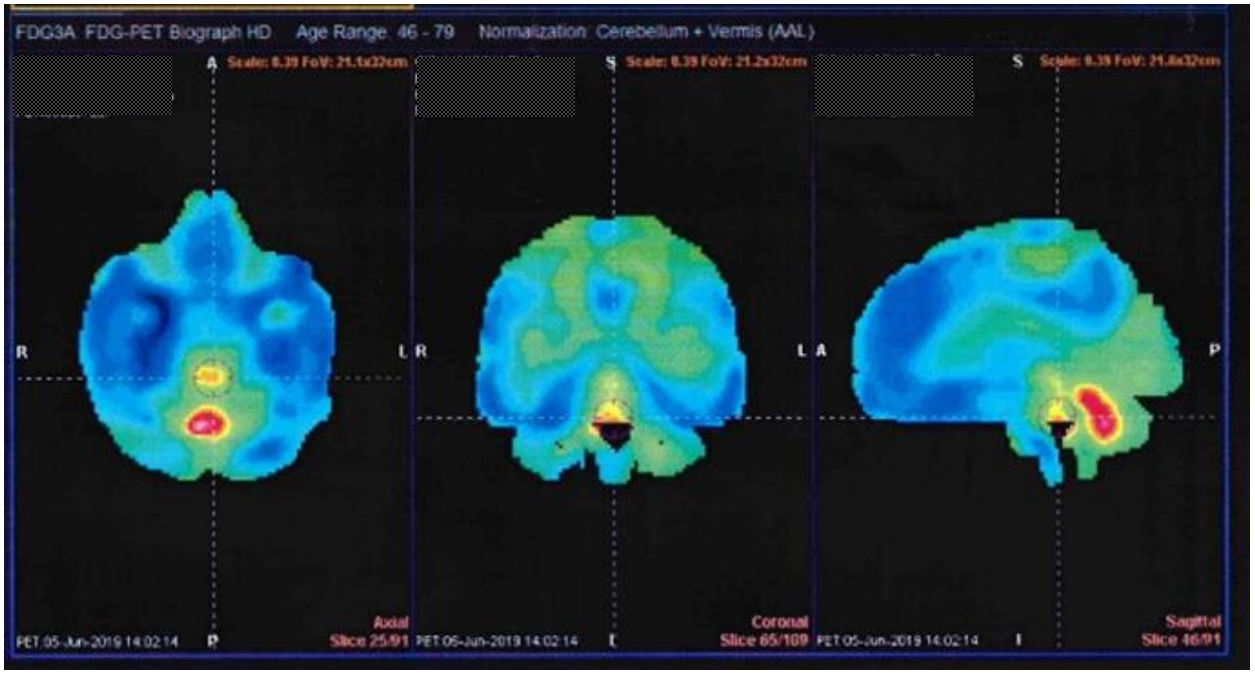
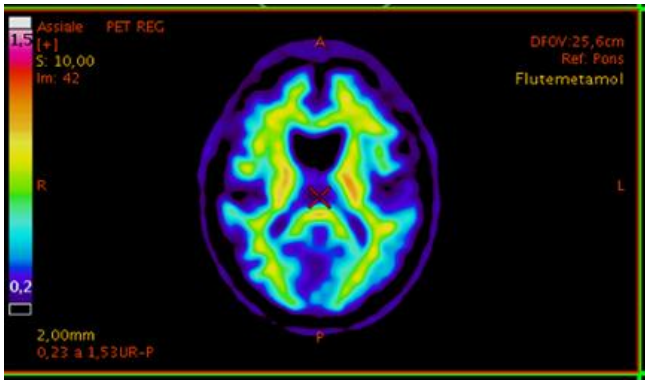
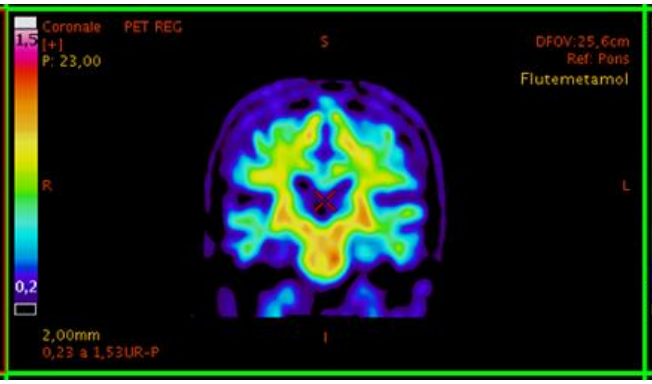
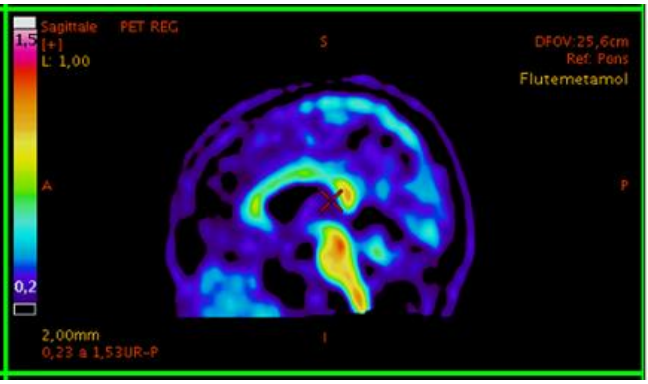



**FDG-PET**

**PET-Amiloide**

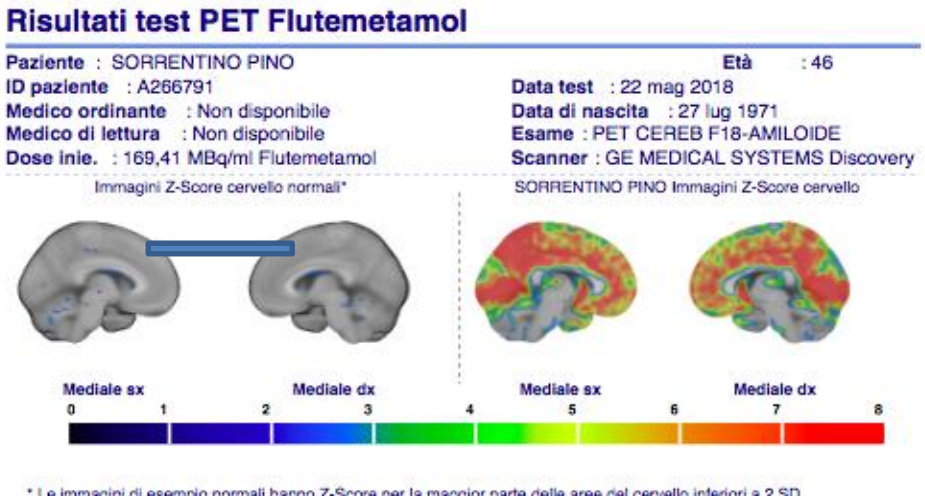


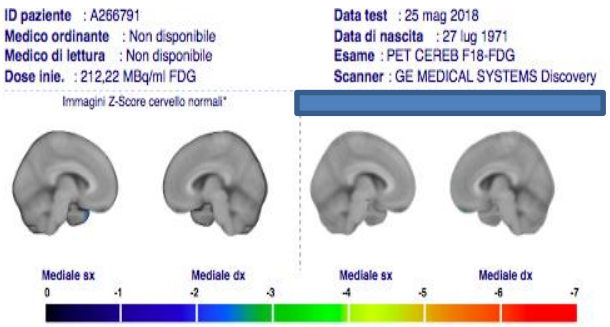



**S P 46 YRS RISK SUBJECT FOR PSEN1MET146LEU- COGNITIVELY HEALTHY**

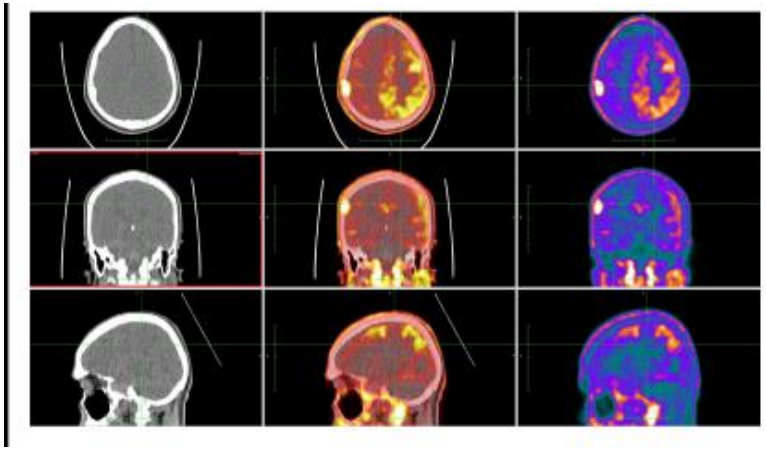
# PET amiloide




# PET FDG




# PET TAU



**S P 47 YRS PS1MET146LEU-**

**Early symptoms**

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Review

# The diagnostic value of FDG and amyloid PET in Alzheimer's disease—A systematic review

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ABSTRACT

*Purpose:* By 2050 it is projected that 115 million people worldwide will have Alzheimer's Disease (AD) [1]. Recent attempts have been made to redefine the diagnostic criteria of AD to include markers of neurodegeneration – measurable by FDG-PET – and markers of amyloid accumulation – measurable by amyloid-PET.
*Materials and methods:* A systematic review of the literature was performed to examine the current diagnostic use of amyloid and FDG PET. MEDLINE and EMBASE databases and the Cochrane Database were searched for relevant papers
*Results and discussion:* This search resulted in twenty-nine papers on amyloid imaging, twenty-three papers on FDG-PET and eight papers which utilized both techniques. Both modalities are considered in turn with regards to their diagnostic accuracy, their role in mild cognitive impairment (MCI) and prognostication, their use in the differential diagnosis of AD and their clinical application. As evidenced from the current literature, both amyloid and FDG-PET meet criteria for suitable biomarkers for the diagnosis of AD. They both indicate pathophysiological processes, albeit at different stages of the Alzheimer's process, and are distinct from normal patterns of aging.
*Conclusion:* Both techniques have been shown to detect AD with high sensitivity and specificity compared to other neurodegenerative processes and cognitively normal age-matched individuals. However, future studies with standardised, uniform thresholds and a lengthier longitudinal follow-up need to be conducted to allow us to make surer conclusions about the future role of PET in clinical practice. In addition, comparison with post-mortem diagnosis, rather than clinical diagnosis with its acknowledged flaws, would result in more powerful statistical outcomes – which is becoming increasingly important given that several disease-modifying AD drugs are now in phase 3 trials.

# Cerebrospinal fluid biomarkers for differentiation of frontotemporal lobar degeneration from Alzheimer's disease

*David J. Irwin[1,2], John Q. Trojanowski[1] and Murray Grossman[2]**

**Frontiers in Aging Neuroscience** February 2013 | Volume 5 | Article 6 | **1**

**Table 1 | Comparative studies of CSF biomarkers in autopsy/genetic-confirmed FTLD and AD cohorts.**

| Study | Patients | $A\beta_{1-42}$ | t-tau | p-$tau_{181}$ | Diagnostic accuracy (AD vs. FTLD) |
|---|---|---|---|---|---|
| Clark et al., 2003 | (10) FTLD(74) AD* 73 (4) CN | AD < FTLD, CN | CN < FTLD < AD | NA | No statistical analysis of FTLD diagnostic accuracy performed |
| Grossman et al., 2005 | 73 (11) FTLD(17) AD13 CN | AD < FTLD, CN | CN, FTLD < AD | CN, FTLD < AD | t-tau<br>AUC = 0.86, sens = 74%, spec = 82.4% |
| Bian et al., 2008 | (30) FTLD(19) AD13 CN | AD < FTLD, CN | CN, FTLD < AD | NA | t-tau/$A\beta_{1-42}$<br>AUC = 0.93, sens = 78.9%, spec = 96.6% |
| Engelborghs et al., 2008 | (2) FTLD(73) AD* 100 CN | NA | NA | NA | No statistical analysis of FTLD diagnostic accuracy performed |
| Koopman et al., 2009 | (10) FTLD(95) AD | AD < FTLD | FTLD < AD | FTLD < AD | p-$tau_{181}$<br>AUC = 0.85, sens = 91%, spec = 80% |
| Tapiola et al., 2009 | (9) FTLD(83) AD | NA | NA | NA | No statistical analysis of FTLD diagnostic accuracy performed |
| Brunnstrom et al., 2010 | (12) FTLD(8) AD* | NA | NA | NA | No statistical analysis of FTLD diagnostic accuracy performed |
| Irwin et al., 2012b | (20) FTLD(41) AD* | NA | NA | NA | t-tau/$A\beta_{1-42}$<br>AUC = 0.99, sens = 90–100%, spec = 90–96% |
| Toledo et al., 2012 | (71) AD(29) FTLD66 CN | AD < FTLD < CN | CN, FTLD < AD | CN, FTLD < AD | t-tau/$A\beta_{1-42}$ (ELISA)<br>AUC = 0.96, sens = 90, spec = 82%<br>p-$tau_{181}$/$A\beta_{1-42}$ (xMAP)<br>AUC = 0.98, sens = 100%, spec = 88% |

# Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease

Niklas Mattsson[1,2,*], Philip S Insel[1,3], Sebastian Palmqvist[1,2], Erik Portelius[4], Henrik Zetterberg[4,5], Michael Weiner[3], Kaj Blennow[4], Oskar Hansson[1,2,**], for the Alzheimer's Disease Neuroimaging Initiative[†]

| Comparison | CSF T-tau | CSF Ng | CSF NFL | Difference T-tau versus Ng | Difference T-tau versus NFL | Difference Ng versus NFL |
|---|---|---|---|---|---|---|
| Associations between neurodegeneration biomarkers and Aβ pathology within diagnostic group | | | | | | |
| CN $A\beta^-$ versus CN $A\beta^+$ | **0.528 (0.0069)** | 0.332 (0.087) | 0.102 (0.60) | 0.197 (0.32) | **0.426 (0.031)** | 0.229 (0.24) |
| MCI $A\beta^-$ versus MCI $A\beta^+$ | **0.824 (< 0.001)** | **0.727 (< 0.001)** | 0.00778 (0.96) | 0.0970 (0.61) | **0.816 (< 0.001)** | **0.719 (0.00015)** |
| AD $A\beta^-$ versus AD $A\beta^+$ | **0.789 (0.040)** | 0.618 (0.11) | −0.632 (0.098) | 0.171 (0.67) | **1.420 (0.00057)** | **1.249 (0.0024)** |
| Associations between neurodegeneration biomarkers and combinations of clinical diagnosis and Aβ pathology | | | | | | |
| CN $A\beta^-$ versus CN $A\beta^+$ | **0.528 (0.0069)** | 0.332 (0.087) | 0.102 (0.60) | 0.197 (0.32) | **0.426 (0.031)** | 0.229 (0.24) |
| CN $A\beta^-$ versus MCI $A\beta^+$ | **0.916 (< 0.001)** | **0.816 (< 0.001)** | **0.798 (< 0.001)** | 0.100 (0.52) | 0.119 (0.45) | 0.0185 (0.91) |
| CN $A\beta^-$ versus AD $A\beta^+$ | **1.172 (< 0.001)** | **0.860 (< 0.001)** | **0.973 (< 0.001)** | **0.312 (0.045)** | 0.199 (0.20) | −0.113 (0.47) |
| CN $A\beta^-$ versus MCI $A\beta^-$ | 0.119 (0.51) | 0.120 (0.51) | **0.633 (0.00067)** | −0.00141 (0.99) | **−0.514 (0.014)** | **−0.513 (0.015)** |
| CN $A\beta^-$ versus AD $A\beta^-$ | 0.494 (0.18) | 0.0564 (0.88) | **1.40 (0.00028)** | 0.438 (0.24) | **−0.909 (0.016)** | **−1.35 (0.00040)** |

# Clinical value of neurofilament and phospho-tau/tau ratio in the frontotemporal dementia spectrum

Lieke H.H. Meeter, MD, Everard G. Vijverberg, MD, Marta Del Campo, PhD, Annemieke J.M. Rozemuller, MD, Laura Donker Kaat, MD, Frank Jan de Jong, MD, Wiesje M. van der Flier, PhD, Charlotte E. Teunissen, PhD, John C. van Swieten, MD, and Yolande A.L. Pijnenburg, MD

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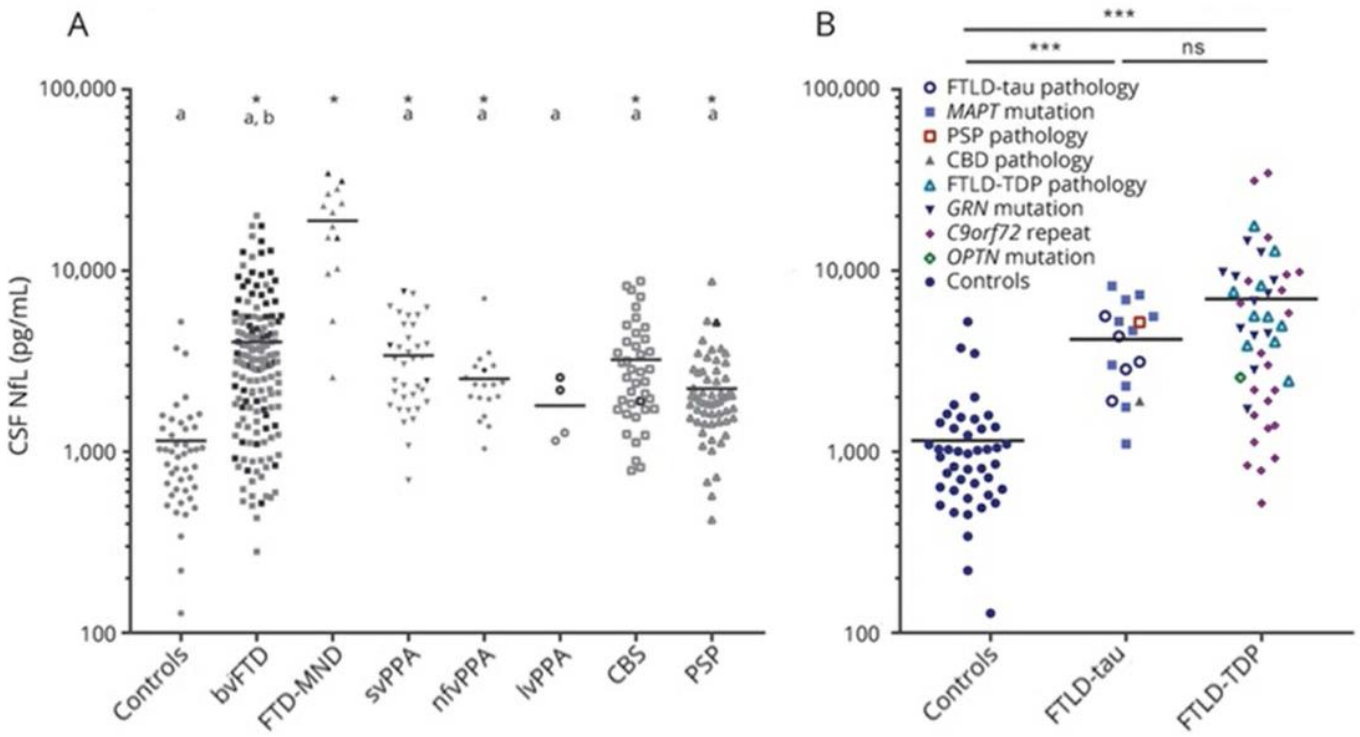
*Neurology*® 2018;90:e1231-e1239. doi:10.1212/WNL.0000000000005261



# Conclusioni

La diagnosi clinica delle demenze è un processo complesso.

La stessa malattia può esprimersi con quadri clinici di esordio differenti.

Lo stesso quadro clinico può essere indotto da patologie diverse.

La pratica quotidiana deve tenere conto della variabilità clinica delle varie forme di demenza al fine di impostare precocemente percorsi diagnostici appropriati